SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acetazolamide Tablets 250 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of Acetazolamide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Acetazolamide Tablets are presented as white flat bevelled edge tablets engraved with R and crescent moon logo on one side and A / 303 either side of a break-line on the other.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acetazolamide is an enzyme inhibitor which acts specifically on carbonic anhydrase. It is indicated in the treatment of:

1. Glaucoma
Acetazolamide is useful in glaucoma (chronic simple (open angle) glaucoma, secondary glaucoma and perioperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure) because it acts on inflow, decreasing the amount of aqueous secretion.

2. Abnormal retention of fluids
Acetazolamide is a diuretic whose effect is due to the effect on the reversible hydration of carbon dioxide and dehydration of carbonic acid reaction in the kidney. The result is renal loss of $HC0^{3-}$ ion which carries out sodium, water and potassium.
It can be used in conjunction with other diuretics when effects on several segments of the nephron are desirable in the treatment of fluid retaining states.

3. Epilepsy
When used in conjunction with other anticonvulsants best results have been seen in petit mal in children. Good results, however, have been seen in both children and adults, with other types of seizures such as grand mal, mixed seizure patterns, myoclonic jerk patterns etc.

4.2 Posology and method of administration

Posology

1. Glaucoma (simple acute congestive and secondary)

Adults: 250 - 1,000mg (1 – 4 tablets) per 24 hours, usually in divided doses for amounts over 250 mg daily.

2. Abnormal retention of fluid (congestive heart failure, drug-induced oedema)

Adults: For diuresis, the starting dose is usually 250 - 375mg (1 – 1½ tablets) once daily in the morning.

If after an initial response, the patient fails to continue to lose oedema fluid, do not increase the dose but allow for kidney recovery by omitting a day.

Best results are often obtained on a regime of 250 - 375mg (1 – 1½ tablets) daily for two days, rest a day and repeat, or merely giving the tablets every other day.

The use of acetazolamide does not eliminate the need for other therapy e.g. digitalis, bed rest and salt restriction in congestive heart failure and proper supplementation with elements such as potassium in drug-induced oedema.

For cases of fluid retention associated with pre-menstrual tension, a daily dose (single) of 125 – 375 mg is suggested.

3. Epilepsy

Adults: 250 – 1000 mg daily in divided doses.

Children: 8 – 30 mg/kg body-weight in daily divided doses, and not to exceed 750 mg/day.

The change from other medication to acetazolamide should be gradual.

Elderly:
Acetazolamide should only be used with particular caution in elderly patients or those with potential obstruction in the urinary tract or with disorders rendering their electrolyte balance precarious or with liver dysfunction.

Method of administration: Oral

4.3 Contraindications

Known hypersensitivity to the active substance acetazolamide, sulfonamides or to any of the excipients listed in section 6.1.

Depressed sodium and/or potassium blood serum levels.

Marked kidney and liver disease or dysfunction.

Suprarenal gland failure, and hyperchloremic acidosis.

Should not be used in patients with hepatic cirrhosis as this may increase the risk of hepatic encephalopathy.

Long term administration is contraindicated in patients with chronic non-congestive angle-closure glaucoma since it may permit organic closure of the angle to occur while the worsening glaucoma is masked by lowered intra-ocular pressure.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for acetazolamide. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Increasing acetazolamide dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. Increasing the dose often results in a decrease in diuresis. Under certain circumstances, however, very large doses have been given in conjunction with other diuretics in order to secure diuresis in complete refractory failure.

When acetazolamide is prescribed for long-term therapy, special precautions are advisable. The patient should be cautioned to report any unusual skin rash.

The occurrence at the treatment initiation of a feverish generalized erythema associated with pustula may be a symptom of acute generalized exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, acetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

Periodic monitoring of blood cell counts and electrolyte levels are recommended. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides. A precipitous drop in formed blood cell elements or the appearance of toxic skin manifestations should call for immediate cessation of acetazolamide therapy.

In patients with pulmonary obstruction or emphysema where alveolar ventilation may be impaired, acetazolamide may aggravate acidosis and should be used with caution.

In patients with a past history of renal calculi, benefit should be balanced against the risks of precipitating further calculi.

Cases of choroidal effusion/detachment have been reported after the use of acetazolamide. Symptoms include acute onset of decreased visual acuity or ocular pain and can occur within hours after initiation of acetazolamide treatment. If choroidal effusion/detachment is suspected, acetazolamide should be discontinued as rapidly as possible.

Non-cardiogenic pulmonary oedema:

Severe cases of non-cardiogenic pulmonary oedema have been reported after taking acetazolamide, also after a single dose (see section 4.8). Non-cardiogenic pulmonary oedema typically developed within minutes to hours after acetazolamide intake. Symptoms included dyspnoea, hypoxia, and respiratory insufficiency. If non-cardiogenic pulmonary oedema is suspected, acetazolamide should be withdrawn, and supportive treatment should be given. Acetazolamide should not be administered to patients who previously experienced non-cardiogenic pulmonary oedema following acetazolamide intake.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

When given concomitantly, acetazolamide modifies the metabolism of phenytoin, leading to increased serum levels of phenytoin. Severe osteomalacia has been noted in a few patients taking acetazolamide in combination with other anticonvulsants. There have been isolated reports of reduced primidone and increased carbamazepine serum levels with concurrent administration of acetazolamide.

Because of possible additive effects, concomitant use with other carbonic anhydrase inhibitors is not advisable.

Acetazolamide is a sulfonamide derivative. Sulfonamides may potentiate the effects of folic acid antagonists. Possible potentiation of the effects of folic acid antagonists, hypoglycaemics and oral anti-coagulants may occur. Concurrent administration of acetazolamide and aspirin may result in severe acidosis and increase central nervous system toxicity. Adjustment of dose may be required when acetazolamide is given with cardiac glycosides or hypertensive agents.

By increasing the pH of renal tubular urine, acetazolamide reduces the urinary excretion of amphetamine and quinidine and so may enhance the magnitude and the duration of effect of amphetamines and enhance the effect of quinidine.

Ciclosporin: Acetazolamide may elevate ciclosporin levels.

Methenamine: Acetazolamide may prevent the urinary antiseptic effect of methenamine.

Lithium: Acetazolamide increases lithium excretion and the blood lithium levels may be decreased.

Sodium bicarbonate: Acetazolamide and sodium bicarbonate used concurrently increases the risk of renal calculus formation.

4.6 Fertility, pregnancy and lactation

Pregnancy
Acetazolamide has been reported to be teratogenic and embryotoxic in rats, mice, hamsters and rabbits at oral or parenteral doses in excess of ten times those recommended in human beings. Although there is no evidence of these effects in human beings, there are no adequate and well-controlled studies in pregnant women. Therefore, acetazolamide should not be used in pregnancy, especially during the first trimester.

Breast-feeding
Acetazolamide has been detected in low levels in the milk of lactating women who have taken this drug. Although it is unlikely that this will lead to any harmful effects in the infant, extreme caution should be exercised when acetazolamide is administered to lactating women.

Fertility
Not available.

4.7 Effects on ability to drive and use machines

Increasing the dose does not increase the diuresis and may increase the incidence of drowsiness and/or paraesthesia. Less commonly, fatigue, dizziness and ataxia have been reported. Disorientation has been observed in a few patients with oedema due to hepatic cirrhosis. Such cases should be under close supervision. Transient myopia has been reported. These conditions invariably subside upon diminution or discontinuance of the medication.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention:
Not known: frequency cannot be estimated from the available data

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Not known	Thrombocytopenia, leukopenia, aplastic anaemia, bone marrow depression, pancytopenia, agranulocytosis****
Metabolism and nutrition disorder	Not known	Metabolic acidosis, electrolyte imbalance* and thirst**
Psychiatric disorders	Not known	Depression, irritability, reduced libido, Occasional instances of confusion
Nervous system disorders	Not known	Paraesthesia, particularly a "tingling" feeling in the extremities, dizziness, headache, occasional instances of drowsiness, convulsions, flaccid paralysis
Eye disorders	Not known	Transient myopia*** , Choroidal effusion, choroidal detachment
Ear and labyrinth disorders	Not known	Impaired hearing and tinnitus
Gastrointestinal disorders	Not known	Melaena, taste disturbance, nausea, vomiting, diarrhoea
Hepatobiliary disorders	Not known	Fulminant hepatic necrosis****, hepatitis or cholestatic jaundice
Skin and subcutaneous tissue disorders	Not known	Urticaria, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis)****, thrombocytic purpura, photosensitivity, acute generalised exanthematous pustulosis (AGEP)
Renal and urinary disorders	Not known	Haematuria, crystalluria****, renal and ureteral colic****, renal lesions, renal failure, calculus formation****, glycosuria, polyuria
General disorders and administration site conditions	Not known	Fever****, fatigue, anaphylaxis****, flushing
Investigations	Not known	Abnormal liver function
Respiratory, thoracic and mediastinal disorders	Not known	Non-cardiogenic pulmonary oedema

*During long-term therapy, metabolic acidosis and electrolyte imbalance may occasionally occur. This can usually be corrected by the administration of bicarbonate.
**Adverse reactions during short-term therapy are usually non-serious.
***This condition invariably subsides upon diminution or withdrawal of the medication.
****Acetazolamide is a sulfonamide derivative and therefore some side-effects similar to those caused by sulfonamides have occasionally been reported.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No specific antidote. Supportive measures with correction of electrolyte and fluid balance. Force fluids.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Carbonic anhydrase inhibitors.
ATC Code: S01EC01

Acetazolamide is an inhibitor of carbonic anhydrase. By inhibiting the reaction catalysed by this enzyme in the renal tubules, acetazolamide increases the excretion of bicarbonate and of cations, chiefly sodium and potassium, and so promotes alkaline diuresis.

Continuous administration of acetazolamide is associated with metabolic acidosis and resultant loss of diuretic activity. Therefore, the effectiveness of Acetazolamide tablets in diuresis diminishes with continuous use.
By inhibiting carbonic anhydrase in the eye, acetazolamide decreases intra-ocular pressure and is therefore useful in the treatment of glaucoma.

5.2 Pharmacokinetic properties

Absorption
Acetazolamide is fairly rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 2 hours after administration by mouth.

Distribution
It has been estimated to have a plasma half-life of about 4 hours. It is tightly bound to carbonic anhydrase and accumulates in tissues containing this enzyme, particularly red blood cells and the renal cortex. It is also bound to plasma proteins.

Elimination

It is excreted unchanged in the urine; renal clearance being enhanced in alkaline urine.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber that are additional to that already included in other sections of the SPC.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dicalcium phosphate
Maize starch
Pregelatinised maize starch
Magnesium Stearate
Sodium starch glycolate Type A

6.2 Incompatibilities

None reported.

6.3 Shelf life

Opaque plastic containers: 36 months.
Blister packing: 24 months.

6.4 Special precautions for storage

Store in container provided and protect from heat, light and moisture.

6.5 Nature and contents of container

1. Opaque plastic containers composed of polypropylene tubes and polyethylene tamper evident closures for pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100 and 112.

3. Blister packs of aluminium/opaque PVC, it is subsequently packed in printed boxboard cartons in pack sizes of 28, 30, 42, 56, 60, 84, 90 and 112.

6.6 Instructions for use/handling

No special instructions for use/handling.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
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Basingstoke,
RG21 8SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 20416/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 January 2004

10 DATE OF REVISION OF THE TEXT

01/11/2024